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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/020,063	BAKER ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 13 December 2001 and 04 August 2002 have been entered in full. Claims 1-27 are cancelled and claims 28-47 are added.

Claims 28-47 are under consideration in the instant application.

Specification

1. The disclosure is objected to because of the following informalities:

2. The disclosure is objected to because it contains numerous embedded hyperlinks and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "DNA ENCODING A TRANSMEMBRANE POLYPEPTIDE".

Appropriate correction is required.

Claim Rejections - 35 USC § 101 and 35 USC § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 28-47 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation.

Specifically, claims 28-47 are directed to an isolated nucleic acid having at least 80%, 85%, 90%, 95%, and 99% nucleic acid sequence identity to (a) a nucleic acid sequence encoding the polypeptide shown in Figure 218 (SEQ ID NO: 374), (b) a nucleic acid sequence encoding the polypeptide shown in Figure 218 (SEQ ID NO: 374) lacking its associated signal peptide, (c) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 218 (SEQ ID NO: 374), (d) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 218 (SEQ ID NO: 374) lacking its associated signal peptide, (e) a nucleic acid sequence shown in Figure 217 (SEQ ID NO: 373), (f) the full-length coding sequence of the nucleic acid sequence shown in Figure 217 (SEQ ID NO: 373), or (g) the full-length coding sequence of the cDNA deposited under ATCC accession number 203465. The claims are directed to an isolated nucleic acid comprising the previously mentioned subparts (a), (b), (c), (d), (e), (f), or (g). The claims also recite a vector and host cell.

The specification discloses that "many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel transmembrane proteins. We herein describe the identification and characterization of a novel transmembrane protein designated herein as PRO1759" (pg 31, lines 22-25). However, the instant specification does not teach any significance or functional characteristics of the PRO1759 polynucleotide (SEQ ID NO: 373) or polypeptide (SEQ ID NO: 374). The specification also does not disclose any methods or

working examples that indicate the polynucleotides and polypeptide of the instant invention are involved in any activity. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO1759. Without any information as to the specific properties of PRO1759, the mere identification of such as being a transmembrane polypeptide is not sufficient to impart any particular utility to the claimed polynucleotides. Since significant further research would be required of the skilled artisan to determine how the claimed polynucleotide and polypeptide are involved in any activities, the asserted utilities are not substantial. Since the utility is not presented in mature form and significant further research is required, the utility is not substantial. The specification asserts the following as patentable utilities for the claimed putative nucleic acid (SEQ ID NO: 373):

1) as hybridization probes for cDNA and genomic DNA (pg 364, lines 25-39)

2) for antisense or sense oligonucleotides (pg 365, lines 2-39; pg 366, lines 1-6)

3) in chromosome and gene mapping/identification (pg 366, lines 7-11; pg 368, lines 8-11)

4) to identify proteins or other molecules involved binding interactions (pg 366, lines 12-22)

5) to generate transgenic or "knock out" animals (pg 366, lines 23-39; pg 367, lines 1-18)

6) in gene therapy (pg 367, lines 19-39; pg 368, lines 1-4)

7) in tissue typing (pg 368, lines 12-15)

Each of these shall be addressed in turn.

1) as hybridization probes for cDNA and genomic DNA. This asserted utility is not substantial or specific. Hybridization probes can be designed from any nucleic acid sequence. Further, the specification does not disclose specific cDNA, DNA, or RNA targets. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

2) for antisense or sense oligonucleotides. This asserted utility is not specific or substantial. Antisense oligonucleotides can be designed from any nucleic acid sequence. Further, the specification does not disclose a specific DNA/RNA target. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

3) in chromosome and gene mapping/identification. This asserted utility is not specific or substantial. Such assays can be performed with any nucleic acid. Further, the specification does not disclose a specific DNA target. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

4) to identify proteins or other molecules involved binding interactions. This asserted utility is not specific or substantial. Such assays can be performed with any nucleic acid. Additionally, the specification discloses nothing specific or substantial for the proteins or other molecules that can be identified by this method. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

5) to generate transgenic or "knock out" animals. This asserted utility is not specific or substantial. The specification does not disclose diseases associated with a mutated, deleted, or

translocated PRO1759 gene (SEQ ID NO: 373). Significant further experimentation would be required of the skilled artisan to identify such a disease. The specification discloses nothing about whether the gene will be "knocked in" or "knocked out" or what specific tissues and cells are being targeted. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

6) in gene therapy. This asserted utility is not specific or substantial. Such can be performed for any nucleic acid. Further, the specification does not disclose diseases associated with a mutated, deleted, or translocated PRO1759 gene (SEQ ID NO: 373). Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease and to determine the route of administration of the gene, as well as quantity and duration of treatment. Since this asserted utility is also not presented in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

7) in tissue typing. This asserted utility is specific or substantial. Such assays can be performed with any nucleic acid. Further, the specification does not disclose specific DNA sequences for use as markers for RFLP, to prepare primers, or to amplify DNA. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

Additionally, at pages 502-503 of the specification, it is disclosed that nucleic acids encoding PRO1759 had a ΔCt value of at least 1.0 for one primary lung tumor (HF-000840), one primary colon tumor (HF-000795), and HF-001296 but not for all tested colon or lung primary tumors or cultured cell lines. At page 495, ΔCt is defined as one unit corresponds to 1 PCR

cycle or approximately a 2-fold amplification relative to normal, two units corresponds to 4-fold amplification, and so on. At pg 498, lines 7-10, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." The Examiner is unable to find, either in the specification or in the art, an explanation of how ΔCt values are calculated, nor what the significance of such are. It is noted that at page 501, lines 28-29, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 502-508 are (a) expressed with values to one one-hundredth of a unit (e.g. 1.32), and (b) varied from a little over 1 to over 4 in some instances. It is not clear how measurements of hundredths of a PCR cycle can be made, nor what the significance of a difference of 1 or 2 or 4 PCR cycles would be. Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO1759 shows a positive correlation with lung cancer or colon cancer, much less that the levels of PRO1759 would be diagnostic of such. Even *if* the data demonstrated a slight increase in copy number of PRO1759 nucleic acids in primary tumors, such would not be indicative of a use of the polynucleotide or encoded polypeptide as a diagnostic agent. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Table 8 of the specification (pg 502-503) shows that PRO1759 tested

slightly positive in only 3 out of 52 lung or colon tumor samples. One skilled in the art would not conclude that such a weak correlation would indicate that PRO1759 is a diagnostic marker for lung or colon cancer for the following reasons. The art recognizes that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy *before* the epithelial cells turn cancerous. See Hittelman (2001, Ann. N. Y. Acad. Sci. 952:1-12), who teach that damaged, *pre-cancerous* lung epithelium is often aneuploid. See especially p. 4, Figure 4. Similarly, aneuploidy was found in morphologically normal colon tissue (Fleischhacker et al., Modern Path., 8:360, 1995; *e.g.*, p. 360, col. 2). Because aneuploid DNA can be found in normal tissue, detection of increased DNA copy number does not necessary mean those cells containing the DNA are cancerous. The gene amplification assay disclosed in the instant specification does not provide a comparison between the lung or colon tumor samples and normal lung or colon epithelium control, and thus it is not clear that PRO1759 is amplified in cancerous lung or colon epithelium more than in damaged (non-cancerous) lung or colon epithelium. Thus, one skilled in the art would not conclude that PRO1759 is a diagnostic probe for lung or colon cancer. Furthermore, the information given in Table 8 was generated using PCR primers that measured amplification of the coding region of SEQ ID NO: 373. However, the claims are broadly drawn to variants of SEQ ID NO: 373, including fragments and degenerate variants which have substitutions relative to SEQ ID NO: 373. One skilled in the art would expect that such variant sequences would lose their specificity as probes for the target sequence. Therefore, even if Applicant were to establish that the gene amplification assay provides utility and enablement for the coding region of SEQ ID NO: 373, the utility and enablement would not convey to the claimed variants.

5. Claims 28-47 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

However, even if the claimed invention is eventually deemed to have a credible, specific and substantial asserted utility or a well established utility, claims 28-33, 36-37, and 41-47 would remain rejected under 35 U.S.C. § 112, first paragraph. The specification teaches that the term "'PRO/number polypeptide' and 'PRO/number' wherein the term 'number' is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants. The PRO1759 nucleic acids and polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods (pg 301, lines 6-8). The specification discloses that a PRO variant polynucleotide or PRO variant nucleic acid sequence is defined as a nucleic acid molecule which encodes an active PRO polypeptide and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence, a full-length native sequence PRO polypeptide sequence lacking the signal peptide, an extracellular domain of a PRO polypeptide, with or without signal peptide, or any other fragment of a full-length PRO polypeptide sequence (pg 302, lines 4-32). However, the specification does not teach any variant, fragment, or derivative of the PRO1759 nucleic acid other than the full-length nucleic acid sequence of SEQ ID NO: 373. The specification also does not teach functional or structural characteristics of the nucleic acid variants, fragments, and derivatives (including the extracellular domain) recited in the claims.

The problem of predicting protein and DNA structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and DNA is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the DNA and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature

Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Additionally, the Examiner has interpreted claim 46 as reading on isolated host cells, as well as host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. The specification of the instant application teaches that PRO1759 gene products (SEQ ID NO: 373) can be expressed in transgenic animals and any technique known in the art may be used to introduce a PTO1759 transgene into animals to produce the founder lines of transgenic animals (pg 366, lines 23-39; pg 367, lines 1-18). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated PRO1759 gene of SEQ ID NO: 373 is demonstrated to express the PRO1759 peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has PRO1759 "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Additionally, for example, the specification discloses that two possible techniques used to introduce a PRO1759 transgene into animals include pronuclear microinjection and gene targeting in embryonic stem cells. However, the literature teaches that the production of

transgenic animals by microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even rarer than random events. Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos, it would have required undue experimentation for the skilled artisan to have made any and all transgenic non-human animals according to the instant invention. Furthermore, regarding gene targeting in embryonic stem cells, the specification does not provide guidance for identifying and isolating embryonic stem cells or for identifying other embryonal cells which are capable of contributing to the germline of any animal. At the time of filing, Campbell et al. teaches that, "in species other than the mouse the isolation of ES cells has proved more difficult. There are reports of ES-like cell lines in a number of species...However, as yet there are not reports of any cell lines which contribute to the germ line in any species other than mouse" (Campbell et al. Theriology 47(1): 63-72; see pg 65, 2nd paragraph). Thus, based on the art recognized unpredictability of isolating and using embryonic stem cells or other embryonal cells from animals other than mice to produce transgenic animals, and in view of the lack of guidance provided by the specification for identifying and isolating embryonal cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have

had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

The specification also discloses that nucleic acids encoding the PRO1759 polypeptide can be used for gene therapy (pg 367, lines 19-39; pg 368, lines 1-4). However, the specification does not teach any methods or working examples that indicate a PRO1759 nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the PRO1759 nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, ¶ 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, ¶ 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express a PRO1759 nucleic acid into the cell of an organism. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express a PRO1759 nucleic acid in the cell of an organism or be able to produce a

PRO1759 protein in that cell. (Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated host cell...").

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen the same for activity, and to generate a transgenic animal expressing the PRO1759 protein and to introduce and express a PRO1759 nucleic acid in a cell of an organism for therapy; the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity and how to introduce a PRO1759 nucleic acid in the cell of an organism to be able produce that PRO1759; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the unpredictability of making transgenic animals and of transferring genes into an organism's cells; and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6. Claims 28-33, 36-37, and 41-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an isolated nucleic acid having at least 80%, 85%, 90%, 95%, and 99% nucleic acid sequence identity to (a) a nucleic acid sequence encoding the polypeptide shown in Figure 218 (SEQ ID NO: 374), (b) a nucleic acid sequence encoding the polypeptide

shown in Figure 218 (SEQ ID NO: 374) lacking its associated signal peptide, (c) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 218 (SEQ ID NO: 374), (d) a nucleic acid sequence encoding the extracellular domain of the polypeptide shown in Figure 218 (SEQ ID NO: 374) lacking its associated signal peptide, (e) a nucleic acid sequence shown in Figure 217 (SEQ ID NO: 373), (f) the full-length coding sequence of the nucleic acid sequence shown in Figure 217 (SEQ ID NO: 373), or (g) the full-length coding sequence of the cDNA deposited under ATCC accession number 203465. The claims also recite an isolate nucleic acid that hybridizes to (a), (b), (c), (d), (e), (f), or (g). The claims recite a vector comprising the nucleic acid and a host cell comprising the vector. The claims do not require that the nucleic acid or polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Additionally, the description of one polynucleotide species (SEQ ID NO: 373) and one polypeptide species (SEQ

ID NO: 374) is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all variants and fragments and with at least 80%, 85%, 90%, 95%, and 99% sequence identity to a nucleic acid comprising the sequence of SEQ ID NO: 375.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid consisting of the sequence of SEQ ID NO: 373, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 28-33, 36-37, and 41-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. The polypeptide identified as PRO1759 is disclosed as having multiple transmembrane domains (see for example, Figure 218), which would result in multiple extracellular domains. Therefore, it is unclear what is meant by the recitation of "**the** extracellular domain" in claims 28-33, 36-37, and 41-47. Further, if the polypeptide had an extracellular domain, the recitation of "the extracellular domain"..."lacking its associated signal sequence" (claim 28, part (d), for example) is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

9. Also, regarding claim 42, stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at

wash conditions of **A** X SSC and **B** % SDS at **C**°C"), claim 42 fails to define the metes and bounds of the varying structures of polynucleotides recited in the claimed methods.

Priority

10. Applicant's claim for priority under 35 U.S.C. 120 and 119(e) is acknowledged. The polynucleotide of SEQ ID NO: 373 and the polypeptide of SEQ ID NO: 374 of the instant application are fully disclosed in the prior applications of 60/108,867 (11/17/1998), PCT/US99/20111 (9/1/1999), 09/403,297 (10/18/1999), PCT/US00/03565 (2/11/2000), PCT/US00/04342 (2/18/2000), and 09/946,374 (9/4/2001). The applications upon which priority is claimed fails to provide adequate support under 35 U.S.C. § 112 for claims 28-47 of this application. Also, the instant specification fails to provide a disclosure meeting the requirements of 35 U.S.C. § 101 and § 112, first paragraph. However, the filing date of 17 November 1998 has been used for the purposes of applying the prior art below.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 28-30 and 41-47 are rejected under 35 U.S.C. 102(e) as being anticipated by LaFleur et al. (U.S. Patent 6,569,992).

LaFleur et al. teach an isolated nucleic acid having at least 91.6% nucleic acid sequence identity to the nucleic acid sequence of SEQ ID NO: 373 of the instant application. (Please see Appendix A attached to this Office Action; see nucleotides 103-1700 of SEQ ID NO: 59 of LaFleur et al. and nucleotides 104-1706 of SEQ ID NO: 373 of the instant application.) LaFleur et al. also disclose that the nucleic acid may be joined to a vector and that the nucleic acid is operably linked to control sequences (col 72, lines 25-36). LaFleur et al. teach that a host cell may comprise the vector and nucleic acid molecule (col 72, lines 44-49; col 73, lines 1-4). LaFleur et al teach that the host cell may be a CHO cell, a yeast cell, or *E. coli*, among others (col 72, lines 49-56). LaFleur et al. teach an isolated nucleic acid that would hybridize to a nucleic acid encoding the polypeptide of SEQ ID NO: 373 under stringent conditions (col 3, lines 1-24). The nucleic acid of LaFleur et al. is at least 10 nucleotides in length. (It is noted that LaFleur et al. first discloses the full length polynucleotide of SEQ ID NO: 59 in provisional application 60/074,157 filed 2/9/1998, and therefore this date has been used for purposes of applying art.)

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Clark et al. Genome Res 13(10) : 2265-2270, 2003 (review discussing the SDPI project).

Strausberg et al. Proc Natl Acad Sci USA 99(26): 16899-16903, 2002 (review of project to identify human and mouse genes).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
15 October 2004

Bridget E. Bunner